UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BOBBY N. GLOVER, LIAN-FENG HUANG, ROBERT W. LANCASTER, STACEY T. LONG, MICHELE C. RIZZOLIO, ERIC A. SCHMITT, and BARRY R. SICKLES

Appeal 2006-2861
Application 10/007,272
Technology Center 1600

ON BRIEF

Before SCHEINER, GRIMES, and LINCK, *Administrative Patent Judges*.

Opinion by GRIMES, *Administrative Patent Judge*. Opinion concurring in part and dissenting in part by LINCK, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition and a treatment method. The Examiner has rejected the claims as anticipated. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

"5,6-Dichloro-2-(isopropylamino)-1-(β-L-ribofuranosyl)-1H-benzimidazole (1263W94) is a benzimidazole derivative useful in medical therapy." (Specification 1.) The specification describes anhydrous crystalline forms and solvates of this compound, pharmaceutical formulations comprising these crystalline forms and solvates, and their use in therapy. (*Id.*)

For example, the specification describes a crystalline form, designated Form II, "defined by the X-ray powder diffraction pattern illustrated in Figure 2" of the application. (*Id.* at 3.) The specification states that "Form II may be produced by crystallization or recrystallization of the amorphous compound . . . from mixtures of methanol and water or methanol and toluene. The initial product of the recrystallization is a methanol solvate which on drying loses methanol to produce Form II." (*Id.*)

The specification states that the crystalline forms and solvates can be used "for the treatment . . . of viral diseases such as herpes virus infections." (*Id.* at 15-16.) The crystalline forms and solvates are preferably administered "as a pharmaceutical formulation," which is generally "prepared by uniformly and intimately bringing in to association the active ingredient with liquid carriers or finely divided solid carriers or both." (*Id.* at 17.) The active ingredient may be included "as a solution or a suspension in an aqueous liquid or a non-aqueous liquid." (*Id.*) The "preparation of dosage forms as solutions of the anhydrous crystalline forms or solvates substantially completely dissolved in a solvent . . . will preclude the

identification of the particular crystalline form utilized in the preparation of the solution." (*Id.* at 18.)

DISCUSSION

1. CLAIMS

Claims 11, 14, and 16-21 are pending and on appeal. We will focus on claims 11 and 14, which are representative and read as follows:

> 11. A pharmaceutical composition comprising a crystalline form of Form II 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole having substantially the same X-ray powder diffraction pattern as Figure 2, wherein said X-ray powder diffraction pattern is obtained with a diffractometer equipped with a diffracted beam curved graphite monochromator using copper Kα X-radiation, and at least one pharmaceutically acceptable carrier therefor.
>
> 14. A method for the treatment of a herpes viral infection in a human which comprises administering to the human host, an effective antiviral amount of a crystalline form of Form II 5,6-dichloro-2 (isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole having substantially the same X-ray powder diffraction pattern as Figure 2, wherein said X-ray powder diffraction pattern is obtained with a diffractometer equipped with a diffracted beam curved graphite monochromator using copper Kα X-radiation.

Thus, claim 11 is directed to a pharmaceutical composition comprising a particular crystalline form (Form II) of the recited compound and at least one pharmaceutically acceptable carrier. Claim 14 is directed to a method for the treatment of herpes viral infection comprising administering crystalline Form II of the recited compound to a human.

Appellants argue that the "pending claims require compositions comprising the specifically recited crystalline form of the compound and

methods comprising administering the compound in the specifically recited crystalline form. . . . [A] composition containing only the compound in solution does not fall within [the] claim language inasmuch as it fails to include the recited crystalline form element of the claim. Similarly, what happens to the drug after ingestion is irrelevant because the [method] claim requires that it is the recited crystalline form of the compound that is administered." (Reply Br. 2.)

We agree with Appellants that the claims require a specifically recited crystalline form of the compound. The specification appears to describe pharmaceutical compositions in which the crystalline form is dissolved in a solvent. (Specification 17-18.) However, we conclude that the language of claim 11 requires that the pharmaceutical composition comprise the recited crystalline form and therefore does not encompass compositions in which the crystalline form is dissolved in a solvent such that the compound is no longer in the crystalline form. Similarly, we conclude that the language of claim 14 requires that the compound be administered to a human in the recited crystalline form.

2. ANTICIPATION

The Examiner has rejected claims 11, 14, and 16-21 under 35 U.S.C. § 102(e) as anticipated by Chamberlain.[1] The Examiner argues that the crystal structure of the active ingredient is "irrelevant" because "i) the pharmaceutical activity of the active ingredient is a function of the molecular structure(s) adsorbed [sic] by the cells contacted by the composition and/or ii) the crystal structure is destroyed by dissolution of the crystalline solid by

[1] Chamberlain et al., U.S. Patent No. 6,077,832, issued June 20, 2000.

the pharmaceutically acceptable carrier." (Answer 3-4.) In particular, the Examiner argues that the claimed compositions have the same biological activity as the prior art composition:

> Therefore, *while the instant claims are not identical with the prior art disclosure*, they are effectively anticipated because the alleged basis for distinction over the prior art, the specific crystalline form of the active ingredient, has no effect whatsoever on the inherent biological activity (anti-herpes virus activity) of the molecules of the active ingredient.

(Answer 4 (emphasis added).)

Appellants argue that the "claimed invention differs from the disclosure of [Chamberlain] in that [the] claims specifically recite a 'crystalline form' of the compound. The rejection improperly ignores this element of the claims." (Br. 3.) "Because the crystalline forms of the compound are novel, compositions and methods of treatment comprising the same novel crystalline forms of the compound are necessarily novel as well." (Br. 4.)

Appellants also argue that it "is wholly irrelevant to the question of anticipation" that "the biological activity of the recited crystalline forms of the compound is no different from the biological activity of the amorphous form of the compound." (Br. 4-5.) Appellants argue that they "are not claiming the biological activity of the compound," but "are claiming pharmaceutical compositions comprising specific crystalline forms of the compound and methods of treatment comprising administration of specific crystalline forms of a compound." (Br. 5.)

We agree with Appellants that the Examiner has failed to set forth a prima facie case of anticipation. Chamberlain describes benzimidazole

derivatives and their use in the treatment "of virus infections such as those caused by herpes viruses," specifically the treatment of humans. (Col. 1, ll. 9-12; col. 5, ll. 47-52.) Chamberlain describes administering the benzimidazole derivatives in a pharmaceutical formulation including one or more carriers. (Col. 7, ll. 45-49.) As the benzimidazole derivative, Chamberlain identifies the compound recited in claims 11 and 14. (Col. 15, ll. 20-21.) However, we agree with Appellants that the Examiner has not set forth a prima facie case that the compound described in Chamberlain has the crystalline form recited in claims 11 and 14.

In particular, we agree with Appellants that the fact that the crystalline forms may have the same biological activity as the amorphous form is "irrelevant to the question of anticipation." Because we conclude that claim 11 is directed to a composition comprising the recited crystalline form of the compound and claim 14 is directed to a method comprising administering the recited crystalline form of the compound, Chamberlain would need to disclose this crystalline form in order to anticipate.

Like claims 11 and 14, the other claims on appeal are directed to compositions comprising, or methods of using, specific crystalline forms or solvates of the recited compound: claims 16 and 17 are directed to compositions comprising the ethanol solvate and Form V, respectively, of the compound; claims 19 and 20 are directed to methods of administering the ethanol solvate and Form V, respectively; and claims 18 and 21 are directed to a composition comprising and a method of using, respectively, a mixture of at least two different specified forms or solvates of the compound.

The Examiner has not set forth a prima facie case that Chamberlain discloses any of the crystalline forms or the ethanol solvate of 5,6-dichloro-2 (isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole. Therefore, we reverse the anticipation rejection.

The dissent argues that "it's reasonable to conclude that at least some portion of Chamberlain's white solid is crystalline and substantially identical to one of the presently claimed crystalline forms of the compound, given identical chemical formulae, synthetic method and activity." We disagree.

First, the "identical chemical formulae" of the claimed and prior art products is irrelevant to patentability in this case because the instant claims are not directed to the compound per se, but to the compound in specific crystalline forms or as an ethanol solvate. The same applies to the assertion that the claimed and prior art products have "identical . . . activity."

The dissent also asserts that the claimed and prior art products are made by an "identical . . . synthetic method." This assertion is factually wrong. The instant specification states that "[t]he compound of formula (I) may be prepared by any method known in the art, but preferably by the methods described in [Chamberlain]" (page 15) but that product is subjected to further "conditions of separation and/or subsequent processing" to produce the claimed crystalline forms or solvate. (*Id.* at 15, ll. 12-14.) See also page 3, ll. 13-15, 23-25; and page 4, ll. 10-14 (describing the processing required to convert the compound of formula (I) into Form II, the ethanol solvate, and Form V, respectively).

In short, neither the Examiner nor our dissenting colleague has cited any evidence to show that Chamberlain's composition would reasonably

have been expected to contain even a single crystal of Form II, Form V, or ethanol solvate of the known compound. While the burden of proof can be shifted to an applicant in appropriate cases, the Office first must show a reasonable basis for concluding that the claims read on the prior art. *See In re Wilder*, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970) ("[I]n an *ex parte* proceeding to obtain a patent, . . . the Patent Office has the initial burden of coming forward with some sort of evidence tending to disprove novelty."); *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) ("[W]hen the PTO shows *sound basis* for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not" (emphasis added).). No such basis has been shown on this record.

SUMMARY

The Examiner has not shown that the claims are anticipated by the applied reference. We therefore reverse the rejection of claims 11, 14, and 16-21.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge) BOARD OF PATENT
) APPEALS AND
Eric Grimes) INTERFERENCES
Administrative Patent Judge)

EBG/MLM

LINCK, Administrative Patent Judge, concurring-in-part and dissenting-in-part

I agree with the majority that the Examiner's anticipation rejection should be reversed. However, the record before us supports a prima facie case of unpatentability under § 102. Thus, a new ground of rejection should be entered.

Appellants are claiming a prior art composition, i.e., 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole in a pharmaceutically acceptable carrier. *See* Chamberlain, Example 5, col. 15, and claim 20. The alleged distinguishing characteristic is in the form of the particles, or crystals. Appellants state that the prior art compound is in an amorphous form, while their compound is in several specific crystalline forms, for example, Form II having "substantially the same X-ray powder diffraction pattern as Figure 2". Spec. at 1-2 & claim 11. Appellants "preferably" synthesize 5,6-dichloro-2-(isopropylamino)1-ß-L-ribofuranosyl-1H-benzimidazole using Chamberlain's synthetic method. Spec. at 15, ll. 1-2. The claimed crystalline forms are then obtained through recrystallization from relatively common solvent systems. For example, Form II is obtained by recrystallizing the allegedly "amorphous" form from methanol and water or methanol and toluene. Spec. at 3, ll. 13-15.

Appellants do not provide any evidence comparing the form of Chamberlain's prior art compound with those now claimed, either in their specification or by declaration. Further, while Appellants assert their crystalline forms "are more thermodynamically stable," "non-hygroscopic," and "have good storage properties" (Spec. at 2), again, they provide no comparative data.

Appellants admit their now-claimed composition has the same biological activity as the prior art composition. Br. 4-5. Appellants argue identity of biological activity is "wholly irrelevant to the question of anticipation." Br. 5. The majority agrees. I do not. Identical activity provides one piece of evidence that the compounds are substantially the same.

Tellingly, Appellants contemplate mixtures of different forms of 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole rather than ones that are in a pure crystalline form, such as Form II:

> The present invention expressly contemplates . . . mixtures of any anhydrous crystalline form or solvate with one or more of the amorphous compound of formula (I) [i.e., 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole] and/or other anhydrous crystalline forms and solvates. It should be understood that admixtures of a particular form or solvate with amorphous compound of formula (I) and/or other crystalline forms or solvates may result in the masking or absence of one or more of the foregoing X-ray powder diffraction peaks . . . for that particular form. Methods are known in the art for analyzing such admixtures of crystalline forms in order to provide for the accurate identification of the presence or absence of particular crystalline forms in the admixture. [Spec. at 13-14. *See also* the language "comprising" in claim 11.]

Thus, Appellants' claims cover an admixture of forms in which the amorphous form predominates and Form II is only present in trace amounts.

Appellants argue their claims "do not encompass compositions or methods comprising non-crystalline forms of the compound." Reply at 2. This argument is inconsistent with their position elsewhere (Spec. at 13-14

(quoted above)) and with the language of their claims. Clearly their "comprising" language encompasses compositions or methods "comprising non-crystalline forms of the compound."

Chamberlain fully discloses and claims 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole in a pharmaceutically acceptable carrier. *See* Example 5, col. 15, and claim 20. Chamberlain purifies the compound using a silica gel column and a chromatron. Col. 15, ll. 25-32. Both purification techniques use a methanol:dichloromethane solvent system (ratio 1:20 and 1:25). *Id.* The resulting compound is a "white solid" and appears to be anhydrous (like the claimed compounds), based on Chamberlain's analytical data. *Id.*; col. 15, ll. 42-43. The term "solid" is also used to describe Appellants' Form II product. *See, e.g.,* Spec. at 22, l. 12.

The term "amorphous" does not appear in Chamberlain. Nor is there any teaching or suggestion that Chamberlain's compound is non-crystalline. Thus, it's reasonable to conclude that at least some portion of Chamberlain's white solid is crystalline and substantially identical to one of the presently claimed crystalline forms of the compound, given identical chemical formulae, synthetic method and activity. And, even if only a trace amount of Chamberlain's "white solid" inherently is in one of the claimed crystalline forms, the claim covering that form is anticipated. *See Smithkline Beecham Corp. v. Apotex,* 403 F.3d 1331, 1339-40, 74 USPQ2d 1398, 1403-04 (Fed. Cir. 2005) (holding that a claim to "Crystalline paroxetine hydrochloride hemihydrate," in essence, would cover a single molecule of hemihydrate, even if not detectable).

It is the Office's responsibility to prevent the issuance of an invalid patent. Yet the Office does not have the facilities to determine what form or admixtures of forms Chamberlain's compound takes. Given the facts of this case, I conclude the record supports a prima facie case of anticipation under 35 U.S.C. § 102.

At this point, Appellants should bear the burden to show they are not claiming something in the prior art and, in this case, for which they may already have a patent.[2] *See, e.g., In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) ("when the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not"). Given the same assignee owns both the Chamberlain patent and the pending application, this burden would not be great. As Appellants observe: "Methods are known in the art for analyzing such admixtures of crystalline forms in order to provide for the accurate identification of the presence or absence of particular crystalline forms in the admixture." Spec. at 14.

Appellants argue the Office has already granted a patent to "the same specific crystalline forms," citing U.S. Patent 6,469,160. Br. 4. I do not believe that fact should have a bearing on our determination with respect to the claims before us in this case. Thus, I have not given it any weight.

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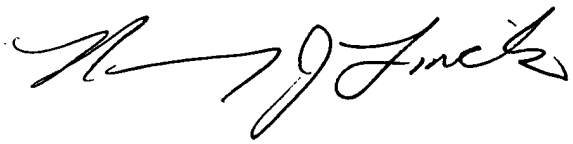
[2] The present application and Chamberlain are owned by the same assignee, SmithKlineBeecham, dba GlaxoSmithKline. Chamberlain will expire no later than July 6, 2015.

Additional Issue Under §103(a)

As noted above, Appellants recrystallized Chamberlain's 5,6-dichloro-2-(isopropylamino)-1-ß-L-ribofuranosyl-1H-benzimidazole from methanol and water or methanol and toluene, solvents commonly used to recrystallize and thereby purify organic compounds. Thus, even if Chamberlain's composition does not inherently anticipate the presently claimed crystalline forms, it seems to me it would have been obvious to the skilled artisan to recrystallize Chamberlain's compound from such solvents in order to further purify it (and likely make it more crystalline).



Nancy J. Linck
Administrative Patent Judge

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GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, MAI B475
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK NC 27709-3398